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SEARCH

Rheumatoid Arthritis

A chronic syndrome characterized by nonspecific, usually symmetric inflammation of the peripheral joints, potentially resulting in progressive destruction of articular and periarticular structures, with or without generalized manifestations.

(See also [Juvenile Rheumatoid Arthritis](#) in Ch. 270.)

Etiology and Pathology

The cause is unknown. A genetic predisposition has been identified and, in white populations, localized to a pentapeptide in the HLA-DR β_1 locus of class II histocompatibility genes. Environmental factors may also play a role. Immunologic changes may be initiated by multiple factors (see also [Autoimmune Disorders under Disorders with Type III Hypersensitivity Reactions](#) in Ch. 148). About 1% of all populations are affected, women two to three times more often than men. Onset may be at any age, most often between 25 and 50 yr.

Prominent immunologic abnormalities that may be important in pathogenesis include immune complexes found in joint fluid cells and in vasculitis. Plasma cells produce antibodies (eg, rheumatoid factor [RF]) that contribute to these complexes. Lymphocytes that infiltrate the synovial tissue are primarily T helper cells, which can produce pro-inflammatory cytokines. Macrophages and their cytokines (eg, tumor necrosis factor, granulocyte-macrophage colony-stimulating factor) are also abundant in diseased synovium. Increased adhesion molecules contribute to inflammatory cell emigration and retention in the synovial tissue. Increased macrophage-derived lining cells are prominent along with some lymphocytes and vascular changes in early disease.

In chronically affected joints, the normally delicate synovium develops many villous folds

The Merck Manual of Diagnosis and Therapy

Section 5. Musculoskeletal And Connective Tissue Disorders

Chapter 50. Diffuse Connective Tissue Disease Topics

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and thickens because of increased numbers and size of synovial lining cells and colonization by lymphocytes and plasma cells. The lining cells produce various materials, including collagenase and stromelysin, which can contribute to cartilage destruction; interleukin-1, which stimulates lymphocyte proliferation; and prostaglandins. The infiltrating cells, initially perivenular but later forming lymphoid follicles with germinal centers, synthesize interleukin-2, other cytokines, RF, and other immunoglobulins. Fibrin deposition, fibrosis, and necrosis also are present. Hyperplastic synovial tissue (pannus) may erode cartilage, subchondral bone, articular capsule, and ligaments. PMNs are not prominent in the synovium but often predominate in the synovial fluid.

Rheumatoid nodules occur in up to 30% of patients, usually subcutaneously at sites of chronic irritation (eg, the extensor surface of the forearm). They are nonspecific necrobiotic granulomas consisting of a central necrotic area surrounded by palisaded mononuclear cells with their long axes radiating from the center, all enveloped by lymphocytes and plasma cells. Vasculitis can be found in skin, nerves, or visceral organs in severe cases of RA but is clinically significant in only a few cases.

Symptoms and Signs

Onset is usually insidious, with progressive joint involvement, but may be abrupt, with simultaneous inflammation in multiple joints. Tenderness in nearly all inflamed joints is the most sensitive physical finding. Synovial thickening, the most specific physical finding, eventually occurs in most involved joints. Symmetric involvement of small hand joints (especially proximal interphalangeal and metacarpophalangeal), foot joints (metatarsophalangeal), wrists, elbows, and ankles is typical, but initial manifestations may occur in any joint.

Stiffness lasting > 30 min on arising in the morning or after prolonged inactivity is common; early afternoon fatigue and malaise also occur. Deformities, particularly flexion contractures, may develop rapidly; ulnar deviation of the fingers with slippage of the extensor tendons off the metacarpophalangeal joints is a typical late result. Carpal tunnel syndrome can result from wrist synovitis. Ruptured popliteal cysts can mimic deep vein thrombosis.

Subcutaneous rheumatoid nodules are not usually an early manifestation. Visceral nodules, vasculitis causing leg ulcers or mononeuritis multiplex, pleural or pericardial effusions, lymphadenopathy, Felty's syndrome, Sjögren's syndrome, and episcleritis are other extra-articular manifestations. Fever may be present and is usually low-grade, except in adult-onset Still's disease, a seronegative RA-like polyarthritis with prominent systemic features.

Laboratory Findings

Blood tests are helpful. A normochromic (or slightly hypochromic)-normocytic anemia, typical of other chronic diseases, occurs in 80% of cases; the Hb is usually > 10 g/dL but may rarely be as low as 8 g/dL. Superimposed iron deficiency or other causes of anemia should be sought if Hb is < 10 g/dL. Neutropenia occurs in 1 to 2% of cases, often with splenomegaly (Felty's syndrome). Mild polyclonal hypergammaglobulinemia and thrombocytosis may be present.

The ESR is elevated in 90% of cases. Antibodies to altered γ -globulin, so-called rheumatoid factors (RFs), as detected by agglutination tests (eg, the latex fixation test uses human IgG adsorbed to particulate latex) that show IgM RF, occur in about 70% of cases. Although RFs are not specific for RA and are found in many diseases (eg, granulomatous diseases, chronic infections, hepatitis, sarcoidosis, subacute bacterial endocarditis), a high RF titer helps confirm the diagnosis. In most laboratories, a latex fixation tube dilution titer of 1:16 is considered the lowest value favoring a diagnosis of RA. RF titers are also often measured by nephelometry (< 20 IU/mL is considered negative). A very high RF titer suggests a worse prognosis and is often associated with progressive disease, nodules, vasculitis, and pulmonary involvement. The titer can be influenced by treatment and often falls as inflammatory joint activity decreases.

The **synovial fluid**, abnormal during active joint inflammation, is cloudy but sterile, with reduced viscosity and usually 3,000 to 50,000 WBCs/ μ L. Of these cells, PMNs typically predominate, but > 50% may be lymphocytes and other mononuclear cells. WBC cytoplasmic inclusions may be seen on a wet smear but are also present in other inflammatory effusions. Synovial fluid complement is often < 30% of the serum level. Crystals are absent.

On **x-ray**, only soft tissue swelling is seen in the first months of disease. Subsequently, periarticular osteoporosis, joint space (articular cartilage) narrowing, and marginal erosions may be present. The rate of deterioration, seen on x-ray and clinically, is highly variable, but erosions as a sign of bony damage may occur within the first year.

Diagnosis

The American College of Rheumatology has developed simplified criteria for the classification of RA (see Table 50-1). Primarily intended as a communication aid for those in clinical research, these criteria can also help guide clinical diagnosis.

Almost any other disease that causes arthritis must still be considered. Some patients with crystal-induced arthritis meet these new criteria; synovial fluid examination often helps exclude these cases. However, two diseases causing arthritis can very occasionally coexist. When diagnosis is in doubt, unexplained subcutaneous nodules can be aspirated or biopsied to differentiate gouty tophi, amyloid, and other causes.

SLE may mimic RA. SLE usually can be distinguished by the characteristic skin lesions of light-exposed areas, temporal-frontal hair loss, oral and nasal mucosal lesions, nonerosive arthritis, joint fluid with often < 2000 WBCs/ μ L (predominantly mononuclear cells), positive antibodies to double-stranded DNA, renal disease, and low serum complement levels (see Systemic Lupus Erythematosus, below). Positive antinuclear antibodies and some features of SLE may occur along with otherwise typical RA, giving rise to the term "overlap syndrome." Some of these patients may have severe RA; others have associated SLE or other collagen disease. Polyarteritis, progressive systemic sclerosis, dermatomyositis, and polymyositis may have features that resemble RA.

Other systemic diseases may cause symptoms similar to RA. Sarcoidosis, amyloidosis, Whipple's disease, and other systemic diseases may involve joints; tissue biopsy sometimes

helps differentiate these conditions. Acute rheumatic fever is differentiated by a migratory pattern of joint involvement and evidence of antecedent streptococcal infection (culture or changing antistreptolysin-O titer). Changing heart murmurs, chorea, and erythema marginatum are much less common in adults than in children. Infectious arthritis usually is monarticular or asymmetric (see Ch. 54). Diagnosis depends on identification of the causative agent. Infection can be superimposed on a joint affected by RA. Gonococcal arthritis usually presents as a migratory arthritis that involves tendons around the wrist and ankle and finally settles in one or two joints. Lyme disease can occur without the classic history of tick bite and rash; it can be screened for serologically (see Ch. 157). Knees are most commonly involved. Reiter's syndrome (reactive arthritis) is characterized by evidence of antecedent urethritis or diarrhea; asymmetric involvement of the heel, sacroiliac joints, and large joints of the leg; urethritis; conjunctivitis; iritis; painless buccal ulcers; balanitis circinata; or keratoderma blennorrhagicum on the soles and elsewhere (see Ch. 51). Serum and joint fluid complement levels are often elevated. Psoriatic arthritis tends to be asymmetric and is not usually associated with RF, but differentiation may be difficult in the absence of characteristic nail or skin lesions (see Ch. 51). Distal interphalangeal joint involvement and arthritis mutilans can be suggestive.

Ankylosing spondylitis may be differentiated by its predilection for males, spinal and axial distribution of joint involvement, absence of subcutaneous nodules, and negative RF test (see Ch. 51). Gout may be monarticular or polyarticular, with complete recovery between acute attacks early in the disease. Chronic gout may mimic RA (see Ch. 55). Typical needlelike or rodlike birefringent monosodium urate crystals with negative elongation are present in the synovial effusion and can be seen by compensated polarized light (see also Ch. 49). Calcium pyrophosphate dihydrate crystal deposition disease may produce monarticular or polyarticular acute or chronic arthritis (see Ch. 55). However, the presence of weakly birefringent rodlike or rhomboid calcium pyrophosphate dihydrate crystals with positive elongation in joint fluid and x-ray evidence of articular cartilage calcification (chondrocalcinosis) differentiate this condition.

Osteoarthritis often involves the proximal and distal interphalangeal joints, first carpometacarpal and first metatarsophalangeal joints, knee joints, and spine (see Ch. 52). Symmetry of involvement, prominent joint swelling (mostly caused by bony enlargement) with some signs of inflammation, joint instability, and subchondral cysts on x-ray may be confusing; the absence of significant amounts of RF, rheumatoid nodules, and systemic involvement along with the characteristic osteoarthritis pattern of joint involvement with synovial fluid WBC counts < 1000 to 2000/ μ L permit differentiation from RA.

Treatment

As many as 75% of patients improve symptomatically with conservative treatment during the first year of disease. However, $\geq 10\%$ are eventually severely disabled despite full treatment. The disease greatly affects the lives of most RA patients.

Rest and nutrition: Complete bed rest is occasionally indicated for a short period during the most active, painful stage of severe disease. In less severe cases, regular rest should be prescribed. Splints provide local joint rest. Joint range of motion and exercise as tolerated must be continued (see below). An ordinary nutritious diet is generally sufficient. Rarely, patients have food-associated exacerbations. Food and diet quackery is common and should

be discouraged. However, fish or plant oil supplements may partially relieve symptoms because they can decrease production of prostaglandins.

Nonsteroidal anti-inflammatory drugs and salicylates: NSAIDs provide important symptomatic relief and may be adequate as simple therapy for mild RA, but they do not appear to alter the long-term course of disease.

Salicylates are relatively safe, inexpensive, analgesic, and anti-inflammatory and can still be a cornerstone of drug therapy. Aspirin (acetylsalicylic acid) is begun with 0.6 to 1.0 g (two to three 300-mg tablets) qid with meals and with a bedtime snack. Dosage may be increased as needed until a maximally effective or mildly toxic dose (eg, tinnitus, diminished hearing) is achieved. The final dose may vary from 3 to 6.0 g/day (about 10 to 20 300-mg tablets). The average daily dose required in active RA is 4.5 g (15 tablets). Antacids, sucralfate, or H₂ blockers between meals can be taken for mild GI symptoms without discontinuing the aspirin. Enteric-coated tablets may offer some advantage because they are less locally irritating in patients with concomitant dyspepsia from gastritis or hiatus hernia. However, absorption may not be as reliable, and systemic actions still affect the gastric mucosa. Misoprostol 100 to 200 µg bid to qid as tolerated used with aspirin (and with the NSAIDs described below) may decrease the chance of erosion and a bleeding gastric ulcer in high-risk patients, but it may cause abdominal cramps and diarrhea and does not relieve nausea or epigastric pain. Proton pump inhibitors also appear to decrease the risk of ulcers. Sustained-release aspirin provides longer relief for some patients and may be useful at bedtime, although patients awakened at night by pain may need a second dose. Nonacetylated salicylates (eg, salsalate, choline magnesium salicylate) seem to offer better GI tolerance than aspirin and do not impair platelet adhesiveness, but they may not be as effective as anti-inflammatory agents.

Other NSAIDs are available for patients who cannot tolerate sufficient aspirin to obtain a good effect or for whom less frequent dosing offers a major advantage (see Table 50-2); these drugs are widely used. Usually, only one such NSAID should be given at a time. Doses of all drugs with flexible dosing can be increased every 2 wk until response is maximal or maximum dosage is reached. Drugs should be tried for ≥ 2 to 3 wk before assuming inefficacy.

Although often less irritating to the GI tract than high-dose aspirin, these other NSAIDs can also produce gastric symptoms and GI bleeding. They should be avoided during active ulcer disease. Other possible side effects include headache, confusion and other CNS symptoms, worsening of hypertension, edema, and decreased platelet adhesiveness. As with aspirin, liver enzymes can be mildly elevated. Creatinine levels can rise because of inhibited renal prostaglandins; less frequently, interstitial nephritis can occur. Patients with urticaria, rhinitis, or asthma from aspirin can have the same problems with these other NSAIDs. Agranulocytosis has been reported.

NSAIDs act by inhibiting cyclooxygenase enzymes and thus inhibit prostaglandins. Some prostaglandins under cyclooxygenase-1 (**COX-1**) control have important effects in many parts of the body (eg, they provide protection to renal blood flow and the gastric mucosa). Other prostaglandins are induced by inflammation and are produced by **COX-2**. Drugs that may inhibit only or predominantly COX-2 (also called coxibs; eg, celecoxib, rofecoxib) may avoid many of the side effects that result from drugs that also inhibit COX-1. Coxibs

have far fewer adverse effects on platelet aggregation and gastric mucosa. However, effects on renal flow are similar to COX-1s.

Slow-acting drugs: The optimal time to add slow-acting drugs to therapy has been re-evaluated, with growing consensus that early use is indicated in persistent disease. Generally, if pain and swelling persist after 2 to 4 mo of disease despite treatment with aspirin or other NSAIDs, the addition of a slow-acting or potentially disease-modifying drug (eg, gold, hydroxychloroquine, sulfasalazine, penicillamine) should be considered. Methotrexate, an immunosuppressive drug (see below), is now increasingly also used very early as one of the second-line potentially disease-modifying drugs.

Gold compounds usually are given in addition to salicylates or other NSAIDs if the latter do not sufficiently relieve pain or suppress active joint inflammation. In some patients, gold may produce clinical remission and decrease the formation of new bony erosions. Parenteral preparations include gold sodium thiomalate or gold thioglucose (aurothioglucose) IM at weekly intervals: 10 mg the first week, 25 mg the second, and 50 mg/wk thereafter until a total of 1 g has been given or significant improvement is apparent. When maximum improvement is achieved, dosage is gradually decreased to 50 mg every 2 to 4 wk. Relapse commonly occurs in 3 to 6 mo if no gold is given after remission. Improvement often can be sustained for several years with prolonged maintenance administration.

Gold compounds are contraindicated in patients with significant hepatic or renal disease or with blood dyscrasia. Before initiating gold therapy, a urinalysis, Hb level, total and differential WBC count, and platelet count should be obtained. These tests should be repeated before each injection during the first month and before every one to two injections thereafter. Presence of HLA-DR3 or HLA-B8 may predict an increased risk of renal and possibly other side effects from both gold and penicillamine. Possible toxic reactions to gold include pruritus, dermatitis, stomatitis, albuminuria with or without a nephrotic syndrome, agranulocytosis, thrombocytopenic purpura, and aplastic anemia. Less common side effects include diarrhea, hepatitis, pneumonitis, and neuropathy. Eosinophilia > 5% and pruritus may precede appearance of a rash and are danger signals. Dermatitis usually is pruritic and ranges in severity from a single eczematous patch to generalized and, very rarely, fatal exfoliation.

Gold should be discontinued when any of the above manifestations appear. Minor toxic manifestations (eg, mild pruritus, minor rash) may be eliminated by temporarily withholding gold therapy, then resuming it cautiously about 2 wk after symptoms have subsided. However, if toxic symptoms progress, gold should be withheld and the patient given a corticosteroid. A topical corticosteroid or oral prednisone 15 to 20 mg/day in divided doses is given for mild gold dermatitis; larger doses may be needed for hematologic complications. A gold chelating drug, dimercaprol 2.5 mg/kg IM, may be given up to four to six times/day for the first 2 days and bid for 5 to 7 days after a severe gold reaction.

A transient nitritoid reaction with flushing, tachycardia, and faintness can occur several minutes after injections of gold sodium thiomalate, particularly if the gold is not stored out of direct light. If these reactions occur, aurothioglucose can be used, as this does not seem to cause nitritoid reactions.

An oral gold compound, auranofin, 3 mg bid or 6 mg once daily, may be tried for >= 6 mo

and, if necessary and tolerated, increased to 3 mg tid for 3 mo more. If the response is not favorable, auranofin should be discontinued. Unlike with injectable gold, diarrhea and other GI symptoms are prominent side effects. Renal and mucocutaneous side effects are fewer than with IM gold, but auranofin does not seem to be as effective as the parenteral gold. Urinalysis, hemoglobin, and the WBC, differential, and platelet counts should be performed at least monthly.

Hydroxychloroquine can also control symptoms of mild or moderately active RA. Toxic effects usually are mild and include dermatitis, myopathy, and generally reversible corneal opacity. However, irreversible retinal degeneration has been reported. Ophthalmologic testing of visual fields using a red test object is recommended before and every 6 mo during treatment. The initial dosage of 200 mg po bid (with breakfast and dinner) is continued for about 6 to 9 mo. The drug should be discontinued if the patient shows no improvement after 6 to 9 mo. If definite improvement is achieved, the dosage can sometimes be decreased to 200 mg/day and continued as long as effective. Frequent eye examinations must be continued.

Sulfasalazine, long used for ulcerative colitis, is now increasingly used for RA (for which it was developed). It is usually given as enteric-coated tablets, starting with 500 mg/day and increasing 500 mg at weekly intervals to 2 to 3 g/day. Benefit should occur within 3 mo. Toxic effects may include gastric symptoms, neutropenia, hemolysis, hepatitis, and rash. Monitoring with CBCs and serum chemistries is important while increasing the dose and occasionally throughout use.

Oral penicillamine may have a benefit similar to gold and may be used in some cases if gold fails or produces toxicity in patients with active RA. Side effects are minimized by starting with low dosages. A dosage of 250 mg/day is given for 30 to 90 days; the dosage is increased to 500 mg/day for another 30 to 90 days and, if definite improvement does not occur, may be increased to 750 mg/day for 60 days. When the patient starts to respond, the dose should not be further increased but kept to the minimally effective level. Before and every 2 to 4 wk during therapy, platelets must be checked and urinalysis and CBC performed. Side effects requiring discontinuation are more common than with gold and include marrow suppression, proteinuria, nephrosis, other serious toxic effects (eg, myasthenia gravis, pemphigus, Goodpasture's syndrome, polymyositis, a lupuslike syndrome), rash, and a foul taste. The drug should be given by, or with guidance from, one experienced with its use, and its effects must be monitored closely.

Combinations of slow-acting drugs may be more effective than a single drug. In a recent trial, hydroxychloroquine, sulfasalazine, and methotrexate together were more effective than methotrexate alone or the other two together.

Corticosteroids: Corticosteroids are the most dramatically effective short-term anti-inflammatory drugs; however, their clinical benefit for RA often diminishes with time. Corticosteroids do not predictably prevent the progression of joint destruction, although a recent report suggested that they may slow erosions. Furthermore, severe rebound follows the withdrawal of corticosteroids in active disease. Because of their long-term side effects, many recommend that corticosteroids should be given only after a careful and usually prolonged trial of less hazardous drugs. Relative contraindications to corticosteroid use include peptic ulcer, hypertension, untreated infections, diabetes mellitus, and glaucoma.

TB should be ruled out before corticosteroid therapy is begun.

Corticosteroids promptly suppress clinical manifestations for many patients and may be used for disease exacerbations to maintain joint function and to allow continued performance of customary duties, but the patient should be cautioned about complications with long-term use. Prednisone dosage should not exceed 7.5 mg/day, except in patients with severe systemic manifestations of RA (eg, vasculitis, pleurisy, pericarditis). Large loading doses followed by rapid dose reduction are not generally recommended (although they have been used), nor is alternate-day therapy, because RA usually is too symptomatic on the days corticosteroids are not given.

Intra-articular injections of corticosteroid esters may temporarily help control local synovitis in one or two particularly painful joints. Triamcinolone hexacetonide may suppress inflammation for the longest time; other depot corticosteroids, including prednisolone tertiary-butylacetate, also are effective. The soluble 21-phosphate preparation of prednisolone or dexamethasone are not recommended because of rapid clearance from the joint and very short duration of action. Overuse of the recently injected, less painful joint may accelerate joint destruction. Because corticosteroid esters are crystalline, local inflammation transiently increases within a few hours in about 2% of injections.

Cytotoxic or immunosuppressive drugs: These drugs (eg, methotrexate, azathioprine, cyclosporine) are increasingly used in management of severe, active RA. They can suppress inflammation and may allow reduction of corticosteroid doses. However, major side effects can occur, including liver disease, pneumonitis, bone marrow suppression, and, after long-term use of azathioprine, malignancy. Patients should be fully informed of these potential side effects, and supervision by a specialist is generally advised.

In the course of severe active disease, methotrexate may be used reasonably early (benefit often occurs in 3 to 4 wk). It can be given 2.5 to 20 mg in a single dose once weekly, starting at 7.5 mg/wk and gradually increased as needed. It should be avoided in heavy drinkers and diabetics. Liver function must be monitored, and a liver biopsy may be needed if liver function tests are abnormal and the patient needs to continue to use this drug. Clinically significant liver fibrosis is uncommon. CBCs should be performed regularly. Pneumonitis is a rare fatal complication. Severe relapses of arthritis can occur after withdrawal. Azathioprine should be initiated at about 1 mg/kg/day (50 to 100 mg) as a single oral dose or bid; dosage can be increased by 0.5 mg/kg/day after 6 to 8 wk at 4-wk intervals to a maximum of 2.5 mg/kg/day. Maintenance should be at the lowest effective dose. Cyclosporine is effective in treatment of RA and may be especially useful in combination with other slow-acting drugs. Dosages generally should not exceed 5 mg/kg/day to minimize toxic effects on BP and renal function. Although not approved for RA in the USA, cyclophosphamide also is effective but is used less often because of greater risks of toxicity.

Etanercept is a tissue necrosis factor antagonist that can be given twice weekly (25 mg sc) to patients who have had an inadequate response to one or more disease-modifying drugs. Experimental therapies (eg, interleukin-1 receptor antagonists) are being studied and have potential but are not yet available.

Exercise, physiotherapy, and surgery: Flexion contractures can be prevented and

muscle strength restored most successfully after inflammation begins to subside. Joint splinting reduces local inflammation and may relieve severe local symptoms. Before acute inflammation is controlled, passive exercise to prevent contracture is given carefully and within the limits of pain. Active exercise (including walking and specific exercises for involved joints) to restore muscle mass and preserve the normal range of joint motion is important as inflammation subsides but should not be fatiguing. Established flexion contractures may require intensive exercise, serial splinting, or orthopedic measures. Orthopedic or athletic shoes with good heel and arch support can be modified using inserts to fit individual needs and are frequently helpful; metatarsal bars placed posteriorly to painful metatarsophalangeal joints decrease the pain of weight bearing.

Although synovectomy only temporarily relieves inflammation, arthroscopic or surgical synovectomy may help preserve joint function if drugs have been unsuccessful. Arthroplasty with prosthetic replacement of joint parts is indicated if joint damage severely limits function: Total hip and knee replacements are the most consistently successful. Prosthetic hips and knees cannot be expected to tolerate resumption of vigorous activities (eg, competitive athletics). Excision of subluxated painful metatarsophalangeal joints may greatly aid walking. Thumb fusions may provide stability for pinch. Neck fusion may be needed for C1-2 subluxation with cord compression or severe pain. Surgical procedures must always be considered in terms of the total disease. Deformed hands and arms limit crutch use during rehabilitation; seriously affected knees and feet prevent full benefit from hip surgery. Reasonable objectives for each patient must be determined, and function must be considered before appearance. Surgery may be performed while the disease is active. Self-help devices enable many patients with severe debilitating RA to perform activities of daily living.